PREVALENCE OF PULMONARY EDEMA IN ACUTE DECOMPENSATED HEART FAILURE: A SYSTEMATIC REVIEW

By

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A Master's Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
in partial fulfillment of the requirements for
the degree of Master of Public Health in
the Public Health Leadership Program

Chapel Hill
2019

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ABSTRACT

Brandon A. Durant: Prevalence of Pulmonary Edema in Acute Decompensated Heart Failure: A Systematic Review
(Under the direction of Patricia Pat-Yue Chang and Cynthia Feltner)

Importance: Accurate and reliable assessment of pulmonary congestion is important for describing baseline characteristics and estimating acute decompensated heart failure (ADHF) patient risk in population studies.

Objective: This systematic review aims to determine prevalence and methods of assessing pulmonary edema in studies enrolling ADHF patients.

Methods: PubMed and Embase were searched from January 2009 to April 2019 to identify studies based on large heart failure registries. Prevalence of ADHF and methods of determining pulmonary edema were abstracted and summarized. The NIH Quality Assessment Tool was used for assessing risk of bias.

Findings: Eight prospective, inpatient, large (N≥1000) heart failure registries were included; all were set in Europe or the US. Although most studies reported using either physical exam or chest radiography for assessment, specific criteria were not generally reported. The prevalence of pulmonary congestion among ADHF patients was imprecise and ranged from 3% to 74%.

Conclusions and Relevance: Large ADHF registries are not consistent at measuring and reporting pulmonary congestion. Use of standardized methods could better estimate the prevalence of pulmonary edema among ADHF populations.

To my mother and family and friends,
I thank you all for your love and continuing support.
You helped me through the worst of times and the best of times.
I dedicate this manuscript to you.
I love you all!

ACKNOWLEDGMENTS

I would like to acknowledge my advisors, Dr. Cindy Feltner, MD, MPH with the RTI-UNC Evidence-Based Practice Center and UNC Gillings School of Global Public Health, and Dr. Patricia Chang, MD, MHS with the UNC Division of Cardiology for supporting my research and writing, as well as guiding me towards the right path academically and professionally. I would also like to acknowledge Dr. Georgette Dent, MD, the Associate Dean for Student Affairs in the UNC School of Medicine, and Dr. Cedric Bright, MD, the former Associate Dean for Inclusive Excellence and Director of the Office of Special Programs in the UNC School of Medicine, now the current Associate Dean of Admissions for the Brody School of Medicine at East Carolina University for both believing in me and supporting me throughout my time during medical school. In addition, I want to give a special acknowledgment to all of the staff at the Office of Special Programs in the UNC School of Medicine for supporting me for almost a decade throughout my undergraduate education and well into my graduate and professional education.

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LIST OF ABBREVIATIONS

ADHF	Acute Decompensated Heart Failure
AHFS	Acute Heart Failure Syndrome
ARIC	Atherosclerosis Risk in Communities Study
COPD	Chronic Obstructive Pulmonary Disease
EMS	Emergency Medical Services
ESC	European Society of Cardiology
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
NIH	National Institutes of Health
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ReDS	Remote Dielectric Sensing

Introduction:

Rationale

Acute decompensated heart failure (ADHF) is a leading cause of hospitalization in patients over 65 years of age. Despite declining in-hospital mortality, 35-40% of patients in the United States and 20-40% in Europe die within a year after discharge[1-3]. Although increased survival rates have been seen over the past four decades with advances in pharmacotherapy and device treatment of heart failure with reduced ejection fraction (HFREF), prevalence of heart failure continues to rise, especially heart failure with preserved ejection fraction (HFPEF)[1,2]. Despite advances in treatment, increasing heart failure prevalence of contributes to high hospitalization rates and, consequently, high health care costs.[3,4] Patients hospitalized with ADHF remain at high risk of both inpatient and post-discharge morbidity and mortality. Therefore, improved diagnosis, monitoring and novel interventions for patients with ADHF represents an important current and future research need.[2] From a public health perspective, the timely and accurate definition, identification and characterization of patients with ADHF is essential for the successful management of population-based heart failure research.[4]

ADHF is diagnosed on the basis of finding a constellation of clinical symptoms and signs, supported by a diagnostic approach that includes laboratory testing and imaging.[5] The presence of pulmonary edema is common in ADHF and has been often used as an entry criterion for heart failure studies.[6] Clinical evidence of pulmonary edema includes rales or crackles on auscultation and findings of pulmonary congestion and/or pleural effusion on chest radiography.[6] Newer, more objective methods of assessing pulmonary edema include pulmonary ultrasound, bioimpedance measurement and remote dielectric sensing (ReDS).[12] However, these are not routinely used in the diagnosis or monitoring of pulmonary edema in population studies.[7-12]

Regardless of whether pulmonary edema is assessed qualitatively using physical exam or imaging, or quantitatively using newer technology, the methods of measurement and criteria to assess pulmonary edema within large epidemiological studies is important to gain a better understanding of its prevalence in ADHF patients. Consistent methods across studies also improves the ability to compare findings. Since severe pulmonary edema with ADHF is associated with a greater mortality risk and rate of hospital readmissions, it is critical to assess pulmonary edema in a systematic and reproducible manner.[13] Accurate and reliable assessment of pulmonary congestion is important for describing baseline characteristics and estimating ADHF patient risk in population studies and in the community, and can be a potentially meaningful outcome in population studies.[14]

Objectives

There has been one previous systematic review without meta-analysis which was published in 2015 that has examined the prevalence and methods of assessment of pulmonary edema in ADHF patients. However, the authors only searched for clinical trials with literature review from 2002-2013.[14] To date, there has not been a systematic review examining the prevalence and methods of assessment of pulmonary edema in large epidemiological studies and heart failure registries. Trials often have narrow inclusion criteria tailored to the intervention being studied. Heart failure registries, however, provide important information on ADHF prevalence, burden, and natural history. This systematic review aims to assess and report the prevalence and methods of assessment of pulmonary edema within ADHF population studies.

Methods:

Reporting guidelines from the PRISMA 2009 checklist for systematic reviews were followed, as noted in Appendix E, Table E1. No registered review protocol exists.

Eligibility Criteria

Eligibility criteria were established a priori, as detailed in Appendix B, Table B1. Inclusion criteria specified adult patients with ADHF. Specifically, definite ADHF is defined as a new onset (de novo) or worsening of a confirmed diagnosis of heart failure based on a combination of a history and physical, imaging, laboratory data, and/or procedures such as electrocardiography or echocardiography, etc., with diuresis as a main treatment for improving symptoms, with no other comorbidities to primarily account for the acute presentation. This definition is based on ARIC Heart Failure Classification criteria[4].

Empirical study designs that were included were intended to capture large heart failure registries in the United States and Europe. The rationale was for better population estimation of pulmonary edema among ADHF patients with comparability among Western nations. These are mainly multi-center, prospective and retrospective cohort studies with at least 1000 registered patients.

Studies occurring in the inpatient and outpatient settings were included. Studies that occurred only in the prehospital or EMS setting were not included. Studies that primarily focus on a singular incitant of ADHF (i.e. acute myocardial infarction, severe hypertension, drug-induced, iatrogenic causes, stress (Takotsubo) cardiomyopathy, etc.) were excluded. Studies that mainly examined suspected or possible ADHF without definitive diagnosis as noted above were excluded.

Additionally, studies that diagnosed acute heart failure solely based on symptoms alone, solely based on physical exam that did not include the presence of crackles or rales, and solely based on laboratory data that did not include B-type natriuretic peptide (BNP) and/or N-terminal pro-BNP were excluded. Studies that only examined chronic heart failure without exacerbation were excluded. Studies that involved pregnant women or peripartum cardiomyopathy were excluded. Finally, studies that did not have any indication of a measurement or prevalence of pulmonary edema or congestion in their study population were excluded.

Literature Search Strategy

The electronic databases PubMed and Embase were searched from January 1, 2009 to April 12, 2019. Basic search eligibility requirements included English language studies published in peer-reviewed journals. Search terms were related to acute decompensated heart failure and pulmonary edema. A full search strategy with complete search terms for these databases can be found in Appendix C, Table C1. Additionally, ClinicalTrials.gov was also searched for grey literature, specifically for unpublished studies with complete results, with the search term, "acute decompensated heart failure". There were no completed studies with unpublished results.

Study Selection Process

Once the search strategy was complete, articles were extracted from their respective databases and organized using EndNote X9[15], with duplicate articles deleted during organization. Abstracts from EndNote X9 were exported then imported into Covidence software[16] for initial article screening by the author. The articles were first screened by title and abstract, then by

review of obtained full text articles, using eligibility criteria established a priori noted previously. The study selection process noted in the PRISMA Flow Diagram in Appendix D, Figure D1.

Data Extraction Process

Data extraction was performed using standardized collection forms, as noted in Appendix A, Tables A1, A2, and A3, to ensure complete and relevant collection.

Abstracted study characteristics included ADHF sample size, geographical region/setting, gender, age, left ventricular ejection fraction (LVEF) by echocardiography, systolic blood pressure, relevant laboratory values (BNP, NT-ProBNP, creatinine), and history of COPD. All of the aforementioned study characteristic items were at study baseline, which was generally at admission into the hospital.

Methods for assessing pulmonary congestion in ADHF patients in these studies were also extracted. Specifically, it was noted whether or not pulmonary congestion was measured with physical exam and/or chest radiography, and if so, which criteria were used for each method.

Prevalence of pulmonary congestion in ADHF patients was extracted based on both physical exam and chest radiography findings, and overall ADHF pulmonary congestion prevalence was determined using these findings and other available reported data from the study (i.e. European Society of Cardiology (ESC) acute pulmonary edema classification, etc.). All methods of assessment and values for prevalence were also at study baseline at the beginning of the patients' hospital admissions. For determining overall prevalence of pulmonary edema at baseline within each study, these values were reported in Appendix A, Table A3 as highest percentage available within the study.

Given the clinical and methodological heterogeneity in the assessment methods as well as the reporting of pulmonary congestion in the reviewed studies, a meta-analysis of the reviewed data could not be performed. No additional analyses were performed.

Risk of Bias in Individual Studies

Individual study risk of bias and overall quality of each study was assessed, as noted in Appendix A, Table A4, using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort Studies.[17]

Risk of Bias Across Studies

Risk of bias across studies and overall strength of evidence was difficult to assess, given the clinical and methodological heterogeneity. It was instead analyzed from the perspective of potential publication bias and possible selective reporting within studies. Reporting within studies was generally compared to determine if information normally presented in the majority of included studies were excluded and, if so, if the authors had justification for its absence.

Results:

Study Selection

Database searches identified 935 articles. After duplicate removal, 699 unique articles were left for screening. There was one additional record identified through hand-searching included studies not captured by our search strategy, totaling 700 articles available for screening. After using eligibility criteria to screen by title and abstract, 669 articles were determined to be irrelevant. The remaining 31 were screened with full text review. After using eligibility criteria to screen during full text review, 11 articles reporting on 8 studies met full eligibility criteria.

The most common reasons for exclusion of full text articles were wrong study design, inadequate sample size, and wrong outcomes. Appendix D, Figure D1 is the PRISMA Flow Diagram which describes the flow for article screening in this systematic review, including reasons for full-text exclusion.

Study Characteristics

The characteristics of the studies for review are shown in Appendix A, Tables A1. Eight large prospective heart failure registries with ADHF patients were eligible for data extraction after article screening. Only one study was from the United States.[23] The other seven studies were from Europe, with three of the seven involving multiple European countries[19,21,22,25] compared to the other four studies which examined one country (Czech Republic[27], Italy[26,28], Romania[18,20], and Spain[24], respectively). Study sample size across studies ranged from n = 1838 to 99,825 patients. All of the study populations came from the inpatient setting; patients were most likely recruited at admission into the hospital for symptoms of ADHF. The study populations were all predominantly male except for one.[24] The age of the patients in the registries ranged from 68.5 to 80.0 years. Left ventricular ejection fraction was typically low in the mid to high 30%. Systolic blood pressure ranged from 130-138 mm Hg across the studies, with the majority of patients presenting with a history of hypertension. BNP / NT-ProBNP was only reported in five of the eight studies, and those that did report them only had values for 50% or less of their study population. In general, BNP / NT-ProBNP were elevated across these studies. Creatinine levels were elevated across all studies from 1.2 to 1.3 mg/dL. A positive history of COPD was reported across the studies for 19% - 35.49% of the study population.

It should be noted that the ESC-HF Pilot study and the ESC-HF-LT study are by the same investigator team. The ESC-HF Pilot study was a precursor to the ESC-HF-LT in terms of

methods used, but each had two different study populations at two different time periods which is why both studies were included for analysis.

The NIH Quality Assessment Tool for Observational Cohort Studies was used to assessing risk of bias. The quality ratings for each study is noted in Appendix A, Table A4. The included studies in general had a good quality rating with a low risk for bias, with the exception of two studies which received fair ratings with a low to medium risk of bias. Across the studies, there was limited selection and measurement bias. For the two studies that received fair ratings, the ESC-HF Pilot and EAFHE studies, respectively, there was some bias for confounders in each study, explained below in Risk of Bias Across Studies.

For each included study, while there was overall limited measurement bias, the measurement of pulmonary edema in the included studies was not clearly defined, equal, valid, and reliable based on reporting, with the exception of the RO-AHFS study which specified physical exam criteria, and the EAHFE study which briefly specified chest radiography criteria.

Methods of Assessment of Pulmonary Congestion

Methods for assessing pulmonary congestion in ADHF patients in these studies were examined. These results are noted in Appendix A, Table A2. Four out of the eight studies reported explicitly using both physical exam and chest radiography findings to assess pulmonary edema.[18-22,27] One study reported solely using physical exam findings for assessment,[26,28] and one study reported only using chest radiography.[24] The remaining two studies did not describe methods for assessing congestion but still reported a prevalence.[23,25]

For the five studies that reported using physical exam findings, each study used rales/crackles as the primary physical exam finding, but only one out of the five studies specified

criteria for what degree of rales would classify as pulmonary edema. The RO-AHFS (2011) study reported that rales more than ½ of the lung fields was considered pulmonary congestion.

For the five studies that reported using chest radiography findings, only two studies explicitly reported any kind of criteria. One study was non-specific, only listing "pulmonary congestion" as a finding. The other study, EAHFE (2018), was more specific and listed "lung interstitial edema" and "lung alveolar edema" as criteria for pulmonary congestion.

Prevalence of Pulmonary Congestion

For the prevalence of pulmonary congestion, these results are noted in Appendix A, Table A3. Only two out of the five studies that reported using physical exam reported a prevalence based on rales or crackles, The ESC-HF-LT study reported a prevalence of 73.6%, and the IN-HF study reported a prevalence of 78%. Additionally, only two out of the five studies that reported using chest radiography reported a prevalence based on presence of pulmonary edema or vascular congestion. The ESC-HF-LT study reported a prevalence of 73.6%, and the EAFHE study reported a prevalence of 58.6% for those with lung interstitial edema and 9.3% for those with lung alveolar edema.

Synthesizing estimates of overall prevalence of pulmonary congestion from included studies was difficult because some studies may have reported pulmonary edema in terms of ESC clinical classification. According to ESC 2008 Guidelines, acute pulmonary edema as a clinical classification of acute heart failure syndrome (AHFS) is characterized as severe breathlessness at rest with crackles or rales over lungs, effusion tachycardia, and tachypnea.[29] This is considered to be a different clinical classification from acute decompensated heart failure, which is its own clinical class under ESC criteria, due to the severity of the pulmonary edema. Four out of the

eight studies (EHFS II, ESC-HF-Pilot, ESC-HF-LT, and RO-AHFS) reported acute pulmonary edema as a separate clinical class similar to the ESC classification system. However, the specific measurement of acute pulmonary edema for these classification purposes in these studies were not reported. Only one out of those four studies (ESC-HF-LT study) also reported pulmonary congestion due to physical exam and chest radiography separate from the ESC classification, which is important since pulmonary congestion can be present in the absence of tachycardia and tachypnea.

For the ESC-HF-LT study, prevalence based on physical exam and chest radiography is reported above, but based on ESC clinical classification, the prevalence of acute pulmonary edema was 13.2%. For the other three studies which reported acute pulmonary edema as a separate clinical class similar to the ESC classification system, the EHFS II, ESC-HF-Pilot, and RO-AHFS studies, the prevalence of acute pulmonary edema based on ESC clinical classification was 13.3%, 16.0%, and 28.7%, respectively. For the EHFS II study, this was the only reported prevalence of pulmonary edema within the study. For the ESC-HF-Pilot study, an additionally reported prevalence of 62% was based on all ADHF patients who presented with pulmonary congestion. However, the method of assessment of pulmonary congestion was not reported in this study. For the RO-AHFS study, the method of assessment of pulmonary congestion was also not reported. However, a prevalence of 60.5% was calculated based on reported percentages of those with pulmonary congestion among their ADHF population, with 59% of those with ADHF with LVEF <45% (n = 1125), and 64.8% of those with ADHF with LVEF >45% (n = 383) having pulmonary congestion. This calculated prevalence is considered the overall prevalence for this study.

The other four studies (GWTG-HF, AHEAD, IN-HF, and EAHFE) did not report acute pulmonary edema as a separate clinical class similar to the ESC classification system. The IN-HF and EAFHE studies' overall prevalence of pulmonary congestion are based on either the highest reported prevalence based on physical exam or chest radiography, noted above. The GWTG-HF reported two different percentages for prevalence, both not related to physical exam or chest radiography criteria and without any other specification of its assessment. Reported prevalence was 3.42% based on pulmonary congestion, which is considered the overall prevalence for this study, and 2.27% if based on acute pulmonary edema that was not specified and not related to ESC classification. The AHEAD study reported an overall prevalence of pulmonary congestion at 18.6%. Although this study did report using crackles on physical exam and chest radiography, it did not specify any specific criteria for exam and imaging, and it did not report prevalence based on physical exam or chest radiography. The specific origin of this prevalence of 18.6% is unclear as there is no other reported specification of its assessment.

Additional Analysis

- No additional analyses were done.

Discussion:

Summary of Evidence

The large ADHF registries in this review were not consistent at measuring and/or reporting pulmonary edema or congestion. Two out of the eight studies did not report at all how they measured pulmonary congestion within their registries. For the other six studies that did report using either physical exam and/or chest radiography for assessment of pulmonary edema,

specific criteria for its assessment was not generally reported. Any methods for assessment of pulmonary edema outside of physical exam and chest radiography were not used in these heart failure registries. Across all of the included heart failure registries, measurement of pulmonary edema was not consistent or standardized.

In addition, with some studies using the ESC classification criteria for acute pulmonary edema without physical exam, chest radiography, or specific criteria, it was difficult to obtain an accurate classification of a) what constitutes pulmonary edema, and b) what constitutes acute decompensated heart failure. Absence of restricting criteria for pulmonary congestion may have resulted in inconsistent classification and overlap between the ESC acute pulmonary edema classification and other ESC clinical classifications of AHFS (i.e. ADHF, cardiogenic shock, hypertensive heart failure, etc.,), leading to lower reported prevalence of pulmonary edema. Other studies grouped and analyzed AHFS together and did not separate the syndromes, which makes it difficult for comparison with studies that do separate the classifications. Without consistent criteria for either pulmonary congestion or ADHF across these studies, it is difficult to compare and contrast and to have an accurate and precise estimation of the prevalence of pulmonary edema in this population. Based on the included studies in this review, the prevalence of pulmonary congestion among ADHF patients in Western countries within United States and Europe imprecisely ranges from about 3% to 74%.

The ability to have standardized definitions of both ADHF and pulmonary congestion across larger studies, as well as standardized assessment of pulmonary edema would most likely result in better estimation of prevalence of pulmonary edema within the ADHF population. This is important for better estimating patient risk, in-hospital and post-discharge mortality in the ADHF population among those exposed to pulmonary congestion.

Lastly, based on this pre-defined search, there is only one recent study investigating pulmonary edema or congestion prevalence status in acute heart failure patients from United States heart failure registries within the past 10 years. During abstract screening and review, there are sub-analyses from United States studies looking at other factors and exposures within AHF patients, but pulmonary edema within this population was not of interest. In the future, there needs to be more studies/registries in the United States that regularly report the prevalence of pulmonary edema within ADHF patients.

Limitations

For the risk of bias across studies, the risk of publication bias is potentially present in terms of studies not being published due to null or non-significant results. Given that this search captured large heart failure registries with overall longitudinal data collection, the chance of a large-scale registry comparable to the eight included studies not being reported or published due to null or unexpected results is not likely. The chance of a similar large-scale prospective study not captured in the pre-determined search strategy is also unlikely.

However, there appears to selective reporting of pulmonary edema within studies. Specifically, as noted above, there were a few studies that appeared to mainly use the ESC clinical class of acute pulmonary edema which is typically reserved for more severe pulmonary edema and make associations with outcomes such as all-cause mortality without making the same associations for those who may have pulmonary congestion present but do not classify for acute pulmonary edema based on ESC classification. Also, the studies that solely report acute pulmonary edema based on ESC classification without other reporting of pulmonary congestion

tended to underreport pulmonary congestion in their studies which could also bias any associations with measured outcomes.

For the two studies that received fair ratings in the NIH Assessment, the ESC-HF Pilot and EAFHE studies, respectively, there was some bias for confounders in each study. Neither study did an adjusted multivariate for their mortality outcome in association with major exposures in their studies for their ADHF patients and thus their reported mortalities should be interpreted cautiously. For the ESC-HF Pilot study, the authors explained that all-cause mortality was not adjusted statistically due to the pilot study's limited number of deaths and the short length of the study (7 months). This was addressed in the later version of the study, the ESC-HF-LT study, which had much more longitudinal data for each patient at 3 months and 1 year. For the EAFHE, there was no apparent justification for the lack of statistical adjustment of its mortality outcome. Every other study reported an adjusted mortality statistic based on reasonable exposures with potential for confounding.

Also, in addition to the characterization of pulmonary edema among these patients, although these registries provide important epidemiological data on acute heart failure, they fail to accurately characterize the population of patients with ADHF due to either a lack of uniform diagnostic criteria across different studies and even different sites within studies. With improvement in consistent training protocols for pulmonary edema within sites and across studies, the characterization of ADHF patients will also improve.

In terms of limitations of this review, given the clinical and methodological heterogeneity in the assessment methods for pulmonary congestion as well as the reporting of pulmonary congestion in the reviewed studies, a meta-analysis of the reviewed data could not be performed.

With improved standardized assessment, criteria, and reporting of pulmonary congestion within ADHF patients in these large heart failure registries, there will be improved pooling of data.

Conclusions

Large epidemiological registries and studies for acute decompensated heart failure are not consistent at measuring and/or reporting pulmonary edema or congestion. There needs to be a standardized method to measure pulmonary edema across large studies for better estimation of prevalence of pulmonary edema in acute heart failure patients.

Future studies and systematic reviews should focus on registries/large studies with follow-up throughout hospitalization from admission to discharge as well as post-hospitalization and follow degree of improvement of pulmonary edema during those time periods with associated pharmacological and interventional therapy. In addition to this, with better standardization of assessment of pulmonary edema, future systematic reviews should examine the pooled association between pulmonary congestion and mortality as well as rehospitalization rates in the inpatient and post-discharge settings.

Finally, with the recent rise in newer quantitative methods and improved technology to assess pulmonary edema, a reliable standard and quantitative method of measuring pulmonary edema in ADHF patients is hopefully in the near future.

Funding:

There was no funding contributed to this review.

APPENDIX A: DATA TABLES

Table A1. Characteristics of Prospective Heart Failure Cohort Studies

Study (year) (n = patients)	GWTG-HF (2016)[23] (n = 99,825)	EHFS II (2010)[22] (n = 2981)	ESC-HF Pilot (2010)[25] (n = 1892)	ESC-HF-LT (2017)[19,21] (n = 6629)	AHEAD (2011)[27] (n = 4153)	IN-HF (2013)[26,28] (n = 1855)	RO-AHFS (2011)[18,20] (n = 1838)	EAHFE (2018)[24] (n = 13,971)
Region								
Male, %	50.85	61.6	62.7	63	57.6	60	60	44.5
Age, years, mean (SD) or median [IQR]	72.63 (14.24)	71.7 [62.3–78.5]	70 (13)	NR (Age >75 years, 34.0%)	73.8 [49.3 - 87.9]	72 (12)	68.5 (12.3)	80.0 (10.1)
LVEF, %, mean (SD) or median [IQR]	NR (49%, 12.8%, and 38.2% had EF <40%, 40% to <50%, and >50%, respectively)	38.4 (15.2)	38 [27 –52]	39.2 (14.5)	37 [16 - 65]	38 (14)	35.6 (12)	51.1 (15.2)
SBP, mmHg, mean (SD) or median [IQR]	NR (80.70% with history of hypertension)	138 [115–160]	133 (29)	130.0 [110–150]	135 [80 - 200]	134 (33)	133.4 (27.6)	NR (83.5% with history of hypertension)
BNP / NT-ProBNP, pg/mL, median [IQR]*	NR	NR	BNP: 870 [423 - 1950] NT-ProBNP: 4007 [2043 - 9487]	BNP: 765 [355 - 1398] NT-ProBNP: 3825 [1658 - 8960]	BNP: 767 [38 - 3,414] NT-ProBNP: 5,294 [285 - 30,000]	BNP: 1112 [542 - 2225] NT-ProBNP: 5168 [2518 - 11583]	NR	BNP: 658 [925] NT-ProBNP: 3892 [6,414]
Creatinine, mg/dL, mean (SD) or median [IQR]	NR (23.95% had creatinine >2)	1.2 [1.0–1.5]	NR (26% had CKD)	1.2 [0.9–1.5]	1.23 [0.77 - 2.73]	1.2 [1.0–1.6]	1.3 (0.6)	1.25 (0.85)
History of COPD, %	35.49	19	NR	19.1	16.2	30	NR	24

Abbreviations: NR = Not Reported; SD = Standard Deviation; IQR = Interquartile Range; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; COPD = chronic obstructive pulmonary disease

*For studies with BNP/NT-ProBNP, data only available for 50% of patients or less

Table A2. Methods of Assessing Pulmonary Congestion in Acute Decompensated Heart Failure Patients

Study (year)	**GWTG-HF (2016)**	**EHFS II (2010)**	**ESC-HF Pilot (2010)**	**ESC-HF-LT (2017)**	**AHEAD (2011)**	**IN-HF (2013)**	**RO-AHFS (2011)**	**EAHFE (2018)**
PC on physical exam (Yes/No?)	No	Yes	No	Yes	Yes	Yes	Yes	No
Physical exam criteria used for PC	N/A	Rales (non-specific)	N/A	Rales (non-specific)	Crackles (non-specific)	Rales (non-specific)	Rales more than 1/2 of the lung fields	N/A
Pulmonary congestion on CXR (Yes/No?)	No	Yes	No	Yes	Yes	No	Yes	Yes
CXR criteria used for pulmonary congestion	N/A	NR	N/A	Pulmonary congestion (non-specific)	NR	N/A	NR	Lung interstitial edema, lung alveolar edema

Abbreviations: NR = Not Reported; N/A = Not Applicable; PC = Pulmonary Congestion; CXR = chest X-ray or chest radiography

Table A3. Prevalence of Pulmonary Congestion in Acute Decompensated Heart Failure Patients

Study (year)	GWTG-HF (2016)	EHFS II (2010)	ESC-HF Pilot (2010)	ESC-HF-LT (2017)	AHEAD (2011)	IN-HF (2013)	RO-AHFS (2011)	EAHFE (2018)
Physical Exam: Rales / Crackles (%)	N/A	NR	N/A	73.6	NR	78	NR	N/A
Pulmonary Edema / Vascular Congestion (%)	N/A	NR	N/A	73.6	NR	N/A	NR	58.6
ADHF Pulmonary Congestion Prevalence (%)	3.42	16	62	73.6	18.6	78	60.5	58.6

Abbreviations: NR = Not Reported; N/A = Not Applicable; CXR = chest X-ray or chest radiography; ADHF = acute decompensated heart failure

ADHF prevalence of pulmonary edema at baseline within each study were reported as highest percentage available within the study

Table A4. NIH Quality Assessment Tool for Observational Cohort Studies

Study (year)	GWTG-HF (2016)	EHFS II (2010)	ESC-HF Pilot (2010)	ESC-HF-LT (2017)	AHEAD (2011)	IN-HF (2013)	RO-AHFS (2011)	EAHFE (2018)
Clearly specified and defined study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participation Rate of Eligible Persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participants selected from similar population, with eligibility criteria prespecified and applied uniformly?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample Size Justification, Power Description, or Variance and Effect Estimates Provided?	No	No	No	No	No	No	No	No
Exposure(s) of Interest Measured Prior to Outcome(s) Being Measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sufficient Timeframe to Reasonably Expect to See An Association Between Exposure and Outcome If It Existed?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Exposure as Categorical or Continuous Variable?	Categorical	Categori	Categorical	Categorical	Categor	Both	Both	Both
Exposure Meausres Clearly Defined, Equal, Valid, and Reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Exposure Assesed More Than Once Over Time?	No	Yes	No	Yes	Yes	Yes	No	Yes
Outcome Meausres Clearly Defined, Equal, Valid, and Reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Investigators Blinded to Exposure Status of Participants?	No	No	No	No	No	No	No	No
Loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confounders appropriately measured and adjusted statistically for impact on relationship between exposure and outcome?	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Quality Rating (Good, Fair, or Poor)	Good	Good	Fair	Good	Good	Good	Good	Fair

APPENDIX B: ELIGIBILITY CRITERIA

Table B1. Eligibility Criteria in PEO* Format

Criteria	Include	Exclude
Population(s)	• Adult US and European patients 18 years and older • Acute decompensated heart failure (ADHF) (both de novo and worsening of chronic HF) based on a combination of H&P, imaging, labs, and/or procedures, with diuresis as a main treatment for improving symptoms, with no other comorbidities to primarily account for presentation	• Non-US or European patients • Less than 18 years old • Studies that primarily focus on one incitant of ADHF (i.e. acute MI, severe hypertension, drug-induced, iatrogenic causes, stress (Takotsubo) cardiomyopathy) • Studies that primarily focus on acute pulmonary edema (APE) • Suspected or possible AHF (want definitive diagnosis) • Chronic heart failure without exacerbation • Pregnant women
Exposure	Tests to Measure Pulmonary Congestion • Physical Exam (must have present crackles/rales) • Imaging Modalities (ultrasound, CXR, CT) • Anything else that is found during the review (novel technology, etc.)	• Studies that solely diagnose HF based on symptoms alone • Studies that solely diagnose HF based on physical exam that does not include present crackles or rales • Studies that solely diagnose HF based on labs that do not include B-type natriuretic peptide (BNP) and/or N-terminal pro-BNP
Outcome(s)	• Primary outcome – Overall prevalence of pulmonary edema / congestion in ADHF patients • Secondary outcomes: • Prevalence of pulmonary edema based on 1) physical exam, 2) imaging, and 3) any other testing	• Studies that do not indicate a prevalence of pulmonary edema or congestion in their study population
Timing	• All studies Jan 2009 and after (capturing 10+ years)	• Studies before Jan 2009
Setting(s)	• Hospitalized patients / inpatient • Non-hospitalized patients / outpatient	• Prehospital setting / EMS
Study Design(s)	• Prospective and retrospective cohort studies • Multi-center studies • Sample size greater than or equal to 1000 participants	• Systematic reviews +/- meta-analyses • RCTs / controlled clinical trials • Cross sectional studies • Case-control studies • Case studies / series / reports • Pilot studies • Background reviews • Comments, editorials, letters, or news articles • Single center studies • Sample size less than 1000 participants
Language	• English	• Not English

*PEO = Population, Exposure, Outcome format, as opposed to the traditional PICO (Population, Intervention, Comparison, Outcome) format.

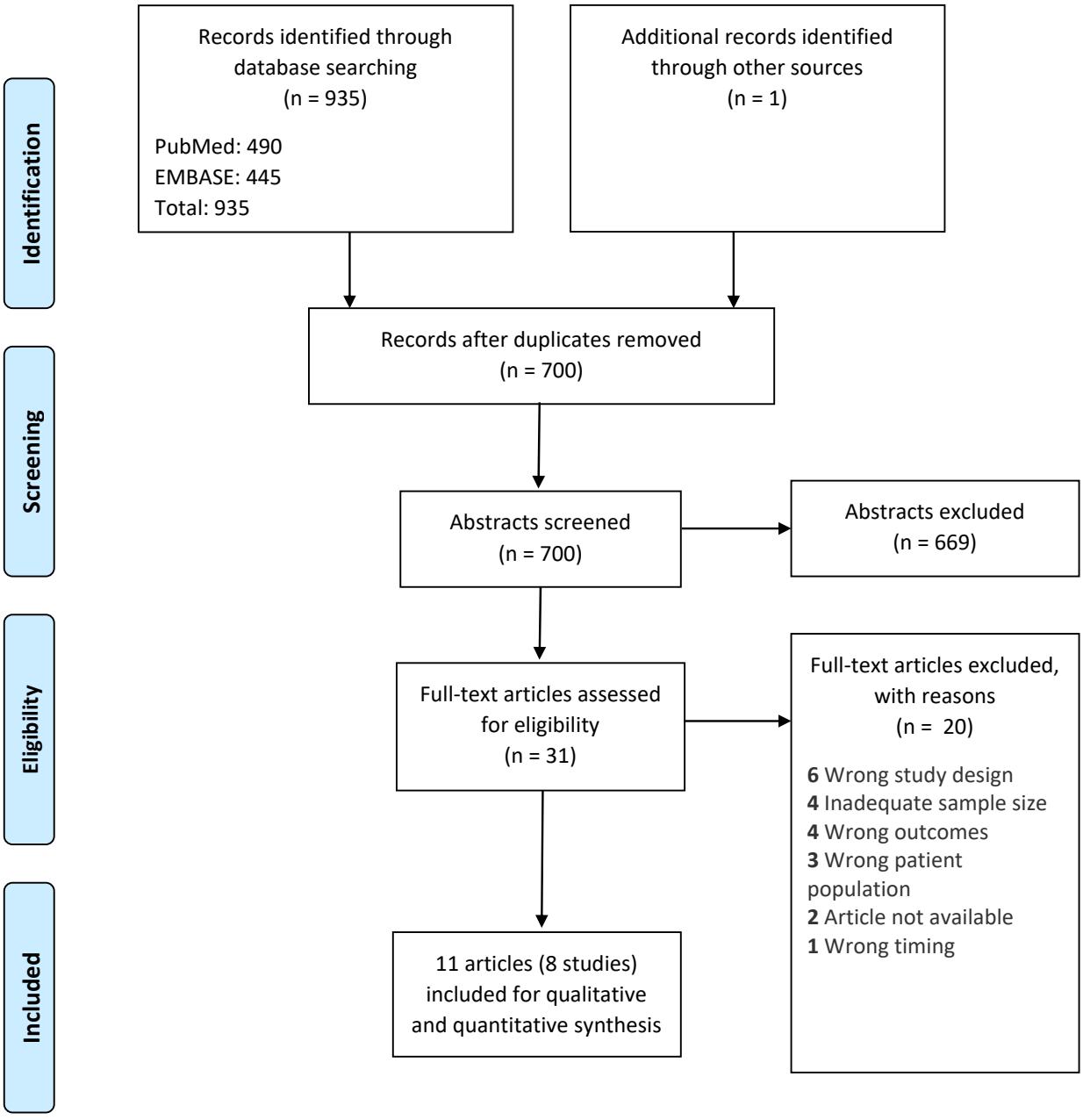
APPENDIX C: SEARCH STRATEGY

Table C1. Search Strategy for PubMed and Embase

PubMed – April 12, 2019		
Search	Query	Results
#1	(heart failure[tiab] AND (decompensated[tiab] OR decompensation[tiab] OR acute[tiab]))	29522
#2	(Pulmonary Edema[mh] OR pulmonary edema[tiab] OR pulmonary edemas[tiab] OR pulmonary oedema[tiab] OR pulmonary congestion[tiab] OR rales[tiab] OR crepitations[tiab] OR crackles[tiab] OR lung fluid[tiab] OR wet lung[tiab] OR wet lungs[tiab] OR cardiogenic edema[tiab] OR cardiogenic oedema[tiab] OR cardiogenic congestion[tiab])	29282
#3	#1 AND #2	1277
#4	#3 AND ("2009/01/01"[PDat] : "2019/12/31"[PDat])	568
#5	#4 AND (English[lang])	519
#6	#5 NOT (animals [mh] NOT humans [mh])	496
#7	#6 NOT (comment[pt] OR commentary[ti] OR editorial[pt] OR editorial[ti] OR letter[pt])	490
Full Search Query	((((((((((heart failure[tiab] AND (decompensated[tiab] OR decompensation[tiab] OR acute[tiab]))))) AND ((Pulmonary Edema[mh] OR pulmonary edema[tiab] OR pulmonary edemas[tiab] OR pulmonary oedema[tiab] OR pulmonary congestion[tiab] OR rales[tiab] OR crepitations[tiab] OR crackles[tiab] OR lung fluid[tiab] OR wet lung[tiab] OR wet lungs[tiab] OR cardiogenic edema[tiab] OR cardiogenic oedema[tiab] OR cardiogenic congestion[tiab]))))) AND ("2009/01/01"[PDat] : "2019/12/31"[PDat])))) AND (English[lang]))) NOT ((animals [mh] NOT humans [mh])))) NOT ((comment[pt] OR commentary[ti] OR editorial[pt] OR editorial[ti] OR letter[pt]))	490
Embase – April 12, 2019		
Search	Query	Results
#1	(((decompensated OR acute OR decompensation) NEXT/5 (heart-failure)):ab,ti)	20200
#2	('lung edema'/exp OR (pulmonary-edema OR pulmonary-edemas OR pulmonary-oedema OR pulmonary-congestion OR rales OR crepitations OR crackles OR lung-fluid OR wet-lung OR wet-lungs OR cardiogenic-edema OR cardiogenic-oedema OR cardiogenic-congestion):ab,ti)	55153
#3	#1 AND #2	1644
#4	#3 AND [2009-2019]/py	1295
#5	#4 AND [english]/lim	1240
#6	#5 NOT ('animal'/exp NOT 'human'/exp)	1209
#7	#6 AND ('article'/it OR 'article in press'/it OR 'review'/it)	445
Full Search Query	(((decompensated OR acute OR decompensation) NEXT/5 'heart failure'):ab,ti) AND ('lung edema'/exp OR 'pulmonary edema':ab,ti OR 'pulmonary edemas':ab,ti OR 'pulmonary oedema':ab,ti OR 'pulmonary congestion':ab,ti OR rales:ab,ti OR crepitations:ab,ti OR crackles:ab,ti OR 'lung fluid':ab,ti OR 'wet lung':ab,ti OR 'wet lungs':ab,ti OR 'cardiogenic edema':ab,ti OR 'cardiogenic oedema':ab,ti OR 'cardiogenic congestion':ab,ti) AND [2009-2019]/py AND [english]/lim NOT ('animal'/exp NOT 'human'/exp) AND ('article'/it OR 'article in press'/it OR 'review'/it)	445

APPENDIX D: PRISMA FLOW DIAGRAM

Figure D1. PRISMA Flow Diagram



Template From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

APPENDIX E. PRISMA CHECKLIST

Table E1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	i (Title)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	iii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	22
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Table E1. PRISMA 2009 Checklist (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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